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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/520,939

**Applicant(s)**

ANDERBERG ET AL.

**Examiner**

ABIGAIL FISHER

**Art Unit**

1616

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 May 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6, 9-11, 15, 19-24, 27, 28 and 32 is/are pending in the application.
- 4a) Of the above claim(s) 4, 6, 9, 10, 15, 21-24, 27 and 32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, 11, 19, 20 and 28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Receipt of Amendments/Remarks filed on May 26 2009 is acknowledged. Claims 7-8, 12-14, 16-18, 25-26, and 29-31 were/stand cancelled. Claim 1 was amended. Claims 1-6, 9-11, 15, 19-24, 27-28 and 32 are pending. Claims 4, 6, 9-10, 15, 21-24, 27 and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 20 2008. Accordingly, claims **1-3, 5, 11, 19-20 and 28** are being examined on the merits herein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-3, 5, 11, 19-20 and 28 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is **withdrawn** in light of Applicants' deletion of solvate and solvate of salt from the claims.

The rejection of claims 1-3, 5, 11, 19-20 and 28 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in light of Applicants' amendments filed on May 26 2009 reciting specific prodrug compounds.

**Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-3, 5, 11, 19-20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Starke et al. (WO 02/32428, "Starke et al. '428", cited on PTO**

**Form 1449** in view of **Starke et al. (WO 02/50051, "Starke et al. '051", cited on PTO Form 1449)** and **Friend et al. (US Patent No. 5811388)**.

### **Applicant Claims**

Applicant claims a combination comprising an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate. A specific IBAT inhibitor claimed is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-1'-(N'-(carboxymethyl)carbamoyl)methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine. A further limitation is that the composition additionally comprises an HMG CoA reductase inhibitor. A further limitation is that the combination is in association with a pharmaceutically acceptable diluent or carrier.

### **Determination of the Scope and Content of the Prior Art (MPEP §2141.01)**

Starke et al. '428 is directed to a pharmaceutical formulation comprising an IBAT inhibitor, an HMG Co-A reductase inhibitor and a therapeutically acceptable carrier which is designed to deliver the IBAT inhibitor into the ileum (abstract and page 1, lines 3-11). IBAT inhibitors taught include 1,4-benzothiazepines and 1-5, benzothiazepines (page 4, lines 28-31). Preferred compounds include those with an oxidized sulphur group, particularly a sulphone in the 7 member ring and the presence of an amine in the 7 member ring (page 5, lines 1-3). HMG Co-A reductase inhibitors are taught as being well known in the art and include fluvastatin, lovastatin, pravastatin, simvastatin, etc. (page 5, lines 6-12). It is taught that the combination of HMG CoA reductase inhibitor will have an additive effect in combination with an IBAT inhibitor on lipid lowering

(column 7, lines 13-14). The core material containing the IBAT inhibitor can be formulated as monolithic tablets, capsules, granules, pellets, etc. The IBAT inhibitor can be mixed with further components such as binders, surfactants, lubricants, etc. (column 8, lines 10-20).

**Ascertainment of the Difference Between Scope the Prior Art and the Claims  
(MPEP §2141.012)**

Starke et al. '428 do not teach that the IBAT inhibitor is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-1'-{N'-(carboxymethyl)carbamoyl)methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine. However, this deficiency is cured by Starke et al. '051.

Starke et al. '051 teach the synthesis of IBAT inhibitors. It is taught that the IBAT inhibitors of the invention can be administered simultaneously, sequentially, or separate administration with an effective amount of an HMG Co-A reductase inhibitor (page 45, lines 7-20). The compositions are taught as being in association with a pharmaceutically acceptable diluent or carrier (page 45, lines 20-30). One specific IBAT inhibitor taught is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-1'-{N'-(carboxymethyl)carbamoyl)methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (example 43).

Starke et al. '428 do not teach that the formulation comprises calcium phosphate. However, this deficiency is cured by Friend et al.

Friend et al. is directed to the delivery of drugs to the lower GI tract. It is taught that one or more excipients may be included in drug formulation to impart satisfactory

processing and compression characteristics and to give additional desirable physical characteristics to the tablets. Mostly the excipients aid in the delayed release of the drug from the composition to achieve regional delivery to the lower GI track (column 11, lines 22-30). It is taught that excipients that are used fulfill several roles, i.e. an excipient that acts as binder to not only increase the hardness but also aid in the delayed release/regional delivery include non-gas forming mineral salts (columns 11-12, lines 60-67 and 1-4). One useful mineral salt is calcium phosphate (column 12, lines 15-16).

***Finding of Prima Facie Obviousness Rationale and Motivation  
(MPEP §2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Starke et al. '428, Starke et al. '051 and Friend et al. and utilize 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-1'-(N'-(carboxymethyl)carbamoyl)methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine as the IBAT inhibitor. One of ordinary skill in the art would have been motivated to utilize 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-1'-(N'-(carboxymethyl)carbamoyl)methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine as Starke et al. '428 teach that the IBAT inhibitors that can be incorporated are preferably 1,5-benzothiazepines with a sulphone and amine in the 7 member ring and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)-1'-(N'-(carboxymethyl)carbamoyl)methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine taught by Starke et al. '051 is an IBAT inhibitor that is a 1,5-benzothiazepine with a sulphone and an amine in the 7 member ring.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Starke et al. '428, Starke et al. '051 and Friend et al. and utilize calcium phosphate in the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to utilize calcium phosphate as Starke et al. '428 teach that the IBAT inhibitor can be mixed with further components such as binders, surfactants, lubricants, etc. and Friend et al. teach that calcium phosphate is an specific binder that not only increases the hardness of the composition but aids in the delayed release and regional delivery profile. Since Starke et al. '428 teach it is desirable to have the IBAT inhibitor released in the ileum, one of ordinary skill in the art would have been motivated to add excipients that aid in the regional delivery profile desired as taught by Friend et al.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicants argue that (1) Starke '428 describes (at page 8) various controlled release formulations of IBAT inhibitors and doesn't reference metal salts and at page 7 describes the possible use of a bile acid binder with colon release as a way to offset diarrhea however this later teaching involves use of a resin not a metal salt. Applicants argue that (2) the list of excipients disclosed in Friend et al. is vast and includes diverse

chemical forms and there is nothing that provides to one deploying IBAT inhibitors which excipients would be appropriate for altering the salvation profile of bile acid liberated when using an IBAT inhibitor.

Applicants' arguments filed May 26 2009 have been fully considered but they are not persuasive.

Regarding applicants' first argument, firstly the examiner does not see where on page 8 Starke '428 describes various controlled release formulations. Page 8 describes how the formulation contains the active compound in admixture with a pharmaceutically acceptable carrier or excipients. Then discussion goes to the preparation of core material containing an IBAT inhibitor. Here specific components taught that are utilized to obtain preferred handling and processing properties include components such as binders, surfactants, lubricants, glidants, etc. However, no specific species of these components are specified. That is why Friend et al. is relied upon. Friend et al. teach specific binders that are known in the art to be utilized in pharmaceutical formulations for GI drug delivery. Secondly, the resin compounds written about on page 7 are not binders in the sense that they bind the components together for tablet formation but binders for binding bile acid thereby reducing bile acids in the colon. Therefore these binders are not the same as the binder excipients taught on page 8. The instant claims recite a combination comprising an IBAT inhibitor and a metal salt wherein the salt is formulated to release in the terminal ileum caecum and/or the colon. IBAT inhibitors taught by Starke '428 include acid-addition salts. Examples of these salts include phosphoric and alkali metal salts with calcium salts being preferred (page 5).

Therefore, Starke '428 suggests the combination of an IBAT and a calcium salt. The calcium salt of the IBAT inhibitor would read on a combination comprising an IBAT inhibitor and a calcium salt. Calcium phosphate would be one acid-addition salt that can be utilized to form the IBAT calcium salt.

Regarding applicants' second argument; firstly the list in Friend et al. is not vast as there are only five excipients taught (polyoxyethylene polymers, silica, calcium phosphate, PVP and cellulosic derivatives). Friend et al. teaches that the invention provides a vehicle for delivering drugs preferentially to the lower GI tract. Various different drugs are listed as suitable indicating many different drugs can be utilized, especially those to be delivered to the GI tract. Secondly, in response to applicant's argument that the excipient would be appropriate for altering the salvation profile of bile acid liberated when using an IBAT inhibitor, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Starke '428 clearly teach the addition of binders to the core of the tablet and calcium phosphate is a well known excipient which is a binder that not only aids in the delayed release profile but also provides for better handling based on the teachings of Friend et al., which is a specific reason taught by Starke '428 to add the excipients (page 8). Thirdly, Starke '428 clearly teaches incorporation of calcium salt in the pharmaceutical formulation as calcium salts of both the IBAT inhibitor and the HMG Co-A reductase inhibitor are taught. Therefore metal salts and calcium salts are clearly contemplated by

Starke '428 in the formulation. Applicants have not demonstrated the unobviousness of the combination of an IBAT and a calcium salt. Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 7192945 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '945 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier. A particular species of formula I is the same as the instantly elected species.

Patent '945 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

Friend et al. is directed to the delivery of drugs to the lower GI tract. It is taught that one or more excipients may be included in drug formulation to impart satisfactory processing and compression characteristics and to give additional desirable physical characteristics to the tablets. Mostly the excipients aid in the delayed release of the drug from the composition to achieve regional delivery to the lower GI track (column 11, lines 22-30). It is taught that excipients that are used that fulfill several roles, i.e. an excipient that acts as binder to not only increase the hardness but also aid in the delayed release/regional delivery include non-gas forming mineral salts (columns 11-12, lines 60-67 and 1-4). One useful mineral salt is calcium phosphate (column 12, lines 15-16).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '945 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate

in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-18 of U.S. Patent No. 7192945 in view of Friend et al. and Starke et al. (WO 02/32428).**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '945 are set forth above.

Patent '945 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

Starke et al. teach that IBAT inhibitors are designed to be delivered into the ileum (abstract and page 1, lines 3-11). It is taught that the combination of HMG CoA reductase inhibitor will have an additive effect in combination with an IBAT inhibitor on lipid lowering (column 7, lines 13-14). HMG Co-A reductase inhibitors are taught as being well known in the art and include fluvastatin, lovastatin, pravastatin, simvastatin, etc. (page 5, lines 6-12).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '945, Friend et al., and Starke et al. and add HMG CoA reductase

inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6906058 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '058 claims a pharmaceutical composition comprising compounds of Va, Vb, VIIa and VIIb or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of Va, Vb, VIIa and VIIb are 1,5-benzodiazapines and are IBAT inhibitors.

Patent '058 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '058 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6906058 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '058 are set forth above.

Patent '058 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '058, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of U.S. Patent No. 7192947 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '947 claims a pharmaceutical composition comprising compounds of formula I or I' or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I or I' are 1,5-benzodiazapines and are IBAT inhibitors.

Patent '947 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '947 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of U.S. Patent No. 7192947 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '947 are set forth above.

Patent '947 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '947, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7192946 in view of Friend et al. Although the conflicting**

**claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '946 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are 1,5-benzodiazapines and are IBAT inhibitors.

Patent '946 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '946 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7192946 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '946 are set forth above.

Patent '946 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '946, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 1-3 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7132416 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '416 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are 1, 2, 5-benzodiazapines and are IBAT inhibitors.

Patent '416 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '416 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7132416 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '416 are set forth above.

Patent '416 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '416, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated

to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Note:** If the elected species is found to be allowable, the obvious type double patenting rejection will be expanded to include claims 3 or 6.

**Claims 1-3 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12 of U.S. Patent No. 7238684 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '684 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are 1, 2, 5-benzodiazapines and are IBAT inhibitors.

Patent '684 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '684 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12 of U.S. Patent No. 7238684 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '684 are set forth above.

Patent '684 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '684, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Note:** If the elected species is found to be allowable, the obvious type double patenting rejection will be expanded to include claims 3 or 6.

**Claims 1-3, 11, 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 13-15 of U.S. Patent No. 7226943 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '943 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. Additionally claimed is a pharmaceutical composition comprising the compounds of formula I and a HMG Co-A reductase inhibitor. The compound is a benzothiepine and a IBAT inhibitor.

Patent '943 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '943 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Note:** If the elected species is found to be allowable, the obvious type double patenting rejection will be expanded to include claims 3 or 6.

**Claims 1-3 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11 of U.S. Patent**

**No. 7125864 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '864 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are IBAT inhibitors.

Patent '864 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '864 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

**Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11 of U.S. Patent No. 7125864 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.**

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '864 are set forth above.

Patent '864 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '864, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

***Response to Arguments***

Firstly, the examiner thanks applicants for pointing out the typo in the previous office action in which the nonstatutory obviousness type double patenting rejection over Patent No. 6906085, 7192946, 7192947, 7132416, 7238684 were indicated as provisional rejections. The examiner has corrected this typo.

Applicants argue that Friend et al. teach a large number of diverse excipients but does not provide any indication that any will be appropriate for use within IBAT inhibitor and provide one of ordinary skill in the art guidance or preference as to which to choose.

Applicants' arguments filed May 26 2009 have been fully considered but they are not persuasive.

Regarding applicants' argument, firstly the list in Friend et al. is not vast as there are only five excipients taught (polyoxyethylene polymers, silica, calcium phosphate, PVP and cellulosic derivatives). Friend et al. teaches that the invention provides a vehicle for delivering drugs preferentially to the lower GI tract. Various different drugs are listed as suitable indicating many different drugs can be utilized, especially those to be delivered to the GI tract. Secondly, in response to applicant's argument that the excipient would be appropriate for altering the salvation profile of bile acid liberated when using an IBAT inhibitor, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte*

*Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Calcium phosphate is a well known excipient which is a binder that not only aids in the delayed release profile but also provides for better handling as taught by Friend et al. which provides the motivation to add it. Thirdly, the recited patents clearly teach incorporation of calcium salt in the pharmaceutical formulation as they recite pharmaceutically acceptable salts of the compounds which include calcium salts. Therefore metal salts and calcium salts are clearly contemplated by the patents in the formulation. Furthermore, the claims recite the salt of the IBAT inhibitors in combination with the HMG Co-A reeducate inhibitor which are also pharmaceutically acceptable salts which include calcium. Applicants have not demonstrated the unobviousness of the combination of an IBAT and a calcium salt. Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

### ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher  
Examiner  
Art Unit 1616

AF

*/Mina Haghighatian/*  
Primary Examiner, Art Unit 1616

